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Evaluation of ‘east-to-west’ ether-forming strategies for the total synthesis of maoecrystal V

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Abstract

Model systems that evaluated different approaches to construct the central ether ring of maoecrystal V are described. Our first model systems attempted the ether formation using C–H functionalization reactions, which led to interesting rearrangements but none of the desired ether product. An intramolecular conjugate addition strategy was then explored that successfully formed the targeted C–O bond but resulted in the undesired stereochemistry.

Keywords

Maoecrystal V; Etherification; Oxy-1,4-addition

In preliminary biological assays maoecrystal V (**3**), a diterpene isolated from the Chinese medicinal herb *Isodon eriocalyx*, was screened against five different human tumor cell lines and found to be selectively active against HeLa cells ($IC_{50} = 60$ nM).¹ In conjunction with this remarkable biological data, the unique and challenging architecture of maoecrystal V (**3**) has generated great interest within the scientific community. The structure of maoecrystal V (**3**) consists of five interwoven carbocyclic rings and six stereogenic centers, two of which are vicinal quaternary centers. This unique topology has driven a number of groups to initiate investigations toward the total synthesis of maoecrystal V (**3**),² with two successful total syntheses reported to date.³

Previously, we disclosed an approach towards maoecrystal V (**3**) that took advantage of sequential Nazarov and Diels–Alder cyclizations to effectively generate the carbocyclic framework of the natural product (i.e., **2**, Figure 1).^{2f}

While generation of this advanced polycyclic species validated the carbon–carbon bond forming reactions used in our approach, significant setbacks arose during attempted installation of the strained ether ring. Our plan for building this ring hinged upon using a remote functionalization reaction to form the ether bond in an “east-to-west” direction from α -hydroxy ketone **4** (Figure 2).⁴ Our initial attempts were complicated by a radical Grob fragmentation that extruded the nitro group and produced an unusual [5.2.2] bicyclic ring system **7**. Herein we report further investigations of this “east-to-west” remote

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Supplementary Material

Experimental procedures, spectral data, and crystallographic data for all new compounds.

functionalization approach, and disclose a new “east-to-west” strategy for ether synthesis based upon an intramolecular oxy-1,4-addition.

To circumvent the problematic Grob fragmentation issue and allow us to investigate the remote functionalization in a simplified setting, the nitro group within **4** was removed using *n*-Bu₃SnH (Figure 3). The thermodynamically more favored enol silane⁵ was then generated in order to regioselectively produce hydroxy ketone **9** by way of a Rubottom oxidation.⁶ Next, a range of conditions were screened to carry out the desired C–H functionalization of **9**. Unfortunately, under no circumstances was ether formation observed. Some unusual reactivity was observed under certain conditions, however. For instance, sunlamp irradiation of hydroxy ketone **9** in the presence of N-iodosuccinimide (NIS)⁷ and NaHCO₃ resulted in the formation of unsaturated lactone **10** as the major product. If the reaction was carried out using a selenurane⁸ and iodine, then the vinyl iodide **11** was obtained. A combination of 2-D NMR spectroscopic studies and X-ray crystallographic evidence was needed to assign the structures of these unexpected products.

Figure 4 presents a possible mechanism to explain the formation of these unusual lactones. The first step likely involves formation of a hypoiodite species, which undergoes homolytic cleavage in the presence of light to afford the oxygen-centered radical **12**. The radical then reacts with the adjacent carbonyl group to furnish the epoxy acetal radical **13**. Cleavage of the carbon–carbon bond results in a ring expansion. Oxidation of the tertiary radical **14** produces the oxocarbenium ion **15**, which is quenched by deprotonation to provide unsaturated lactone **10**.⁹ Vinyl iodide **11** is presumably formed by iodination of **10** with iodine. Barton and coworkers observed related reactivity during their work on the remote functionalizations of steroids.¹⁰

We speculated that significant ring strain developing in the transition state for H–atom abstraction was preventing the desired pathway from proceeding. As such, hydroxy lactone substrates were investigated, as we believed that the six-membered lactone would engender less strain than the five-membered cyclic ketone in the H–atom abstraction transition state. To probe this notion, we designed a model compound (i.e., **16**) that would allow us to rapidly assess the feasibility of such an approach (Figure 5A). Spirocycle **20** was synthesized in 67% yield from cyclohexanone (**18**) according to the two-step protocol reported by RajanBabu and Nugent (Figure 5B).¹¹ Hydroxylation of lactone **20** using MoOPH¹² completed the synthesis of the C–H functionalization precursor **16**. Under a variety of conditions, however, none of the desired ether was observed. Conditions without iodine returned starting material untouched. Using NIS⁷ or diacetoxyiodobenzene (PIDA)¹³ as the oxidant led to varying amounts of decomposition. Interestingly, irradiation of a mixture of lead (IV) acetate (Pb(OAc)₄),⁴ iodine, and hydroxy lactone **16** in cyclohexane or benzene yielded methyl ketone **23** in almost quantitative yield. A possible mechanism for the formation of ketone **23** is shown.

The model system was modified to investigate a new strategy for installing the central ether ring by way of an intramolecular oxy-1,4-addition, rather than the unproductive C–H functionalization route (Figure 6A). Cyclic acetal **28** was prepared in analogy to the preparation of **16** (see Figure 5B), and then converted to TBS ether **29**. Acetal protecting group removal followed by a Saegusa oxidation of ketone **30** resulted in an inseparable 1:1 mixture of diastereomeric enones (i.e., **31**). Further oxidation produced the conjugate addition precursor, dienone **32**. Conditions were then screened to remove the TBS group in the hope that the liberated hydroxyl group would spontaneously cyclize due to its proximity to the enone. Unfortunately, exposure of **32** to trifluoroacetic acid (TFA), tetrabutyl ammonium fluoride (TBAF), or hydrogen fluoride (HF) instead led to the formation of phenol **33**, presumably by way of a dienone–phenol rearrangement.¹⁴ The free tertiary

alcohol could be isolated under appropriate conditions (see Supporting Information), but all attempts to induce cyclization in a second step resulted in either decomposition or the unwanted formation of phenol **33**. Because of the facility that dienone **32** aromatized, the 1:1 mixture of mono-enones **31** was examined in regard to the conjugate addition. To our delight, treatment of siloxy enone with TBAF provided a 64% yield of ether **35** (based on 50% conversion of the 1:1 mixture of isomeric starting materials). This was the first instance of efficient ether bond formation we observed and so we were therefore disappointed that X-ray crystallographic analysis of the product revealed that the addition had proceeded to afford the incorrect stereochemistry. At this juncture it is unclear whether or not the same issue would arise in more advanced intermediates en route to the actual natural product, but our results indicate that some caution is likely warranted if such a strategy were to be undertaken. In fact, the recently reported total synthesis of maoecrystal V completed by Peng and Danishefsky utilized a related east-to-west etherification that also provided the incorrect stereochemistry, thereby necessitating significant steps to correct the issue.¹⁵

In summary, our investigations have revealed numerous complications with the “east-to-west” ether bond construction strategy. Because of this, we have begun examining alternative strategies that install the desired ether with the correct stereochemistry at an early stage of the synthesis. The results of these ongoing investigations will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. Installation of the correct ether stereochemistry has proven to be problematic in a number of approaches pursued by other groups. For illustrative examples and educational discussions, see: refs 2d, 2h, 2j, and 3b.

Figure 1.
Our previous report towards maoecrystal V (3).

Figure 2.
Previous C–H functionalization attempts (P = TBS).

Figure 3.
C–H functionalization attempts in the absence of the nitro group (P = TBS).

Figure 4.
Possible mechanism for the formation of **10** and **11**.

A: Concept for simplified model system **B: Synthesis and reactivity of the C–H functionalization model system**

Figure 5.
Simplified C–H functionalization model system.

A: Concept for oxy-1,4-addition approach **B: Successful ether formation through oxy-1,4-addition**

Figure 6.
An alternative “east-to-west” strategy (P = TBS).